

BIOGRAPHICAL SKETCH

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NAME: Xiang, Yan

eRA COMMONS USER NAME (credential, e.g., agency login): xiangy

POSITION TITLE: Associate Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

| INSTITUTION AND LOCATION | DEGREE (if applicable) | Completion Date MM/YYYY | FIELD OF STUDY |
|--|---------------------------|----------------------------|-----------------------|
| University of Science and Technology of China, Hefei, China | B.S. | 1992 | Molecular Biology |
| Case Western Reserve University, Cleveland, Ohio | Ph.D. | 1997 | Virology/Biochemistry |
| National Institute of Allergy and Infectious Diseases, NIH, Bethesda, Maryland | Post-doc | 1998-2002 | Virology |

A. Personal Statement

I have a vast experience in various aspects of virology including viral replication, immune evasion, and pathogenesis. As a graduate student at Case Western Reserve University, I carried out research on budding and maturation mechanism of retroviruses. As a postdoctoral fellow at the National Institute of Allergy and Infectious Diseases, I worked on immune evasion mechanisms of poxviruses and discovered poxvirus interleukin-18 binding protein. I have continued working on poxvirus immune evasion mechanism since I joined the faculty of my current institute. As the PI of several previous university- and NIH-funded grants, I successfully administered the projects, collaborated with other researchers, and produced several peer-reviewed publications from each project. I have the experience training postdoctoral fellows and students at both M.S. and Ph.D. levels. In summary, I have a demonstrated record of leading successful and productive research projects and mentoring trainees.

B. Positions and Honors.**Positions and Employment**

1998-2002 Research Fellow, Laboratory of Viral Diseases, NIAID, NIH
 2002-2010 Assistant Professor of Microbiology & Immunology, Univ. of Texas HSC at San Antonio
 2010- Associate Professor (with tenure) of Microbiology & Immunology, Univ. of Texas HSC at San Antonio

Other Experience and Professional Memberships

2003-2016 Ad hoc reviewer for various NIH Study Sections, including Virology (VIRA, VIRB), Immunology and Vaccine study
 2011- Academic Editor for PLoS ONE
 2015- Journal of Virology editorial board member
 Ad hoc Reviewer for: PNAS, PLoS Pathogen, NAR, Virology, Antiviral Therapy, Virology Journal, Journal of General Virology

Honors

- 1999 ASBMB/PABMB Graduate/Postdoctoral Travel Award.
- 2001 Honorable Mention Recipient of Norman P. Salzman Memorial Award in Virology, Foundation for NIH.
- 2002 Staff Recognition Award of NIAID/NIH

C. Contribution to Science

1. As a graduate student, I participated in the seminal discovery of the retrovirus 'Late' assembly domain, which is essential for a late step during retroviral budding. I went on to define one of the first molecular motifs for L domains, the classical 'PPPY' motif in Rous sarcoma virus. L domain-mediated budding mechanism was subsequently found to be used by many other viruses. Some of my early papers have been cited over 200 times.
 - a. Wills JW, Cameron CE, Wilson CB, **Xiang Y**, Bennett RP, Leis J. 1994. An assembly domain of the Rous sarcoma virus Gag protein required late in budding. *J. Virol.* 68(10):6605-18. PMID: 8083996. Cited by 253
 - b. **Xiang Y**, Cameron CE, Wills JW, Leis J. 1996. Fine mapping and characterization of the Rous sarcoma virus Pr76gag late assembly domain. *J Virol.* 70(8):5695-700. PMID: 8764091. Cited by 160.
 - c. **Xiang Y**, Ridky TW, Krishna NK, Leis J. 1997. Altered Rous sarcoma virus Gag polyprotein processing and its effects on particle formation. *J Virol.* 71(3):2083-91. PMID: 9032340
 - d. Kikonyogo A, Bouamr F, Vana ML, **Xiang Y**, Aiyar A, Carter C, Leis J. 2001. Proteins related to the Nedd4 family of ubiquitin protein ligases interact with the L domain of Rous sarcoma virus and are required for gag budding from cells. *Proc Natl Acad Sci U S A.* 98(20):11199-204. PMID: 11562473. Cited by 202.
2. As a postdoctoral fellow in Bernie Moss' lab, I discovered the first viral protein that specifically binds and inhibits interleukin-18 (IL-18), an effector of the inflammasome. In my own lab, we further determined the mechanism by which the viral and human IL-18 binding proteins (IL-18BPs) inhibit IL-18. In collaboration with Dr. Junpeng Deng, we have determined two IL-18BP:IL-18 complex structures and have demonstrated how two divergent IL-18BPs target the same surface of IL18 to block receptor binding. Our publications have revealed novel strategies of immune modulations by pathogens and provided knowledge for developing drugs against inflammatory diseases.
 - a. **Xiang Y**, B. Moss. 1999. IL-18 binding and inhibition of interferon gamma induction by human poxvirus-encoded proteins. *Proc. Natl. Acad. Sci. USA.* 96:11537-42
 - b. **Xiang Y**, B. Moss. 2001. Determination of the Functional Epitopes of Human IL-18 Binding Protein by Site-Directed Mutagenesis. *J. Biol. Chem.* 276(20):17380-6.
 - c. Krumma B., Meng X, Li Y., **Xiang Y***, and Deng J* (*Co-corresponding authors). 2008. Structural basis for antagonism of human interleukin 18 by poxvirus interleukin 18-binding protein. *Proc. Natl. Acad. Sci. USA.* 105(52):20711-20715. PMCID: PMC2634891
 - d. Krumm B, Meng X, Wang Z, **Xiang Y***, Deng J*. (*Co-corresponding authors). 2012. A unique bivalent binding and inhibition mechanism by the yatapoxvirus interleukin 18 binding protein. *PLoS Pathog.* 2012 Aug;8(8):e1002876. PMID: 22927815
3. My lab has revealed novel strategies of interferon antagonisms by pathogens. We discovered in vaccinia virus (VACV) two intracellular inhibitors of type I interferons (IFN), K1 and C7. We further showed that K1 and C7 antagonize Interferon-regulatory factor 1-induced antiviral activities. We showed that the C7 function is evolutionarily conserved in all poxviruses that replicate in mammalian cells. We determined the crystal structures of K1 and C7, revealing their mechanisms in antagonizing host restriction factors.
 - a. Meng X, Jiang C, Arsenio J, Dick K, Cao J, **Xiang Y**. 2009. Vaccinia virus K1L and C7L inhibit antiviral activities induced by type I interferons. *J Virol.* 83(20):10627-36. PMCID: PMC2753149
 - b. Li Y, Meng X, **Xiang Y***, Deng J* (*Co-corresponding authors). 2010. Structure function studies of vaccinia virus host-range protein K1 reveal a novel functional surface for ankyrin-repeat proteins. *J Virol.* 84(7):3331-8. PMCID: PMC2838116

- c. X Meng, Schoggins J, Rose L, Cao J, Ploss A, Rice CM and **Xiang Y**. 2012. C7L Family of Poxvirus Host-range Genes Inhibit Antiviral Activities Induced by Type I Interferons and Interferon Regulatory Factor 1. *J Virol*. 86(8):4538-47. PMID: 22345458
 - d. Meng X, Krumm B, Li Y, Deng J*, **Xiang Y***. (*Co-corresponding authors) 2015. Structural basis for antagonizing a host restriction factor by C7 family of poxvirus host-range proteins. *Proc Natl Acad Sci U S A*. 112(48):14858-63. PMID: 26578811
4. My lab has discovered a key component of the poxvirus membrane biogenesis machinery. We identified a poxvirus protein, A6, as essential for poxvirus membrane biogenesis and the trafficking of viral membrane proteins to viral replication factories. We further showed that A6 works together with several other components of poxvirus membrane biogenesis machinery, including A11 and H7. We determined the crystal structure of the H7 protein, revealing a unique and virus-specific PI3P/PI4P-binding domain. We showed that DNA viruses encode specific proteins to hijack cellular phosphoinositides.
- a. Meng X, A. Embry, D. Sochia, **Y. Xiang**. 2007. Vaccinia virus A6L encodes a virion core protein required for formation of mature virion. *Journal of Virology*. 81(3):1433-43. PMID: 17108027
 - b. X Meng, Embry A, Rose L, Yan B, Xu C and **Xiang Y**. 2012. Vaccinia Virus A6 is Essential for Virion Membrane Biogenesis and Localization of Virion Membrane Proteins to Sites of Virion Assembly. *J Virol*. 86(10):5603-13. PMID: 22398288
 - c. M Wu X, Meng X, Yan B, Rose L, Deng J, **Xiang Y**. 2012. Vaccinia virus virion membrane biogenesis protein A11 associates with viral membranes in a manner that requires the expression of another membrane biogenesis protein, A6. *J Virol*. 86(20):11276-86. PMID: 22875972
 - d. Kolli S, Meng X, Wu X, Shengjuler D, Cameron CE, **Xiang Y***, Deng J*. (*co-corresponding author). 2015. Structure-function analysis of vaccinia virus H7 protein reveals a novel phosphoinositide binding fold essential for poxvirus replication. *J Virol*. 89(4):2209-19. PMID: 25473060. This article was selected by the editors of the journal as an article of significant interest.
5. My lab has developed novel methods for generating monoclonal antibodies (mAbs) against native VACV antigens. Using this method, we developed one of the largest panels of mAbs recognizing a variety of VACV proteins in their native conformation in infected cells, most of which were major antigens in the smallpox vaccine and/or proteins involved in virion assembly. Among the mAbs, we have identified novel neutralizing mAbs that target conserved orthopoxvirus antigens previously not known to be neutralization targets. These antibodies also allowed us to study B cell epitopes in the smallpox vaccine and facilitated the development of a novel computation method for predicting B cell epitope. In addition, we have provided our antibodies to many researchers around the world.
- a. Meng X, Zhong Y, Embry A, Yan B, Lu S, Zhong G, and **Xiang, Y**. 2011. Generation and characterization of a large panel of murine monoclonal antibodies against vaccinia virus. *Virology*. 409(2):271-9. PMID: 21056889
 - b. Kaever T, Meng X, Matho MH, Schlossman A, Li S, Sela-Culang I, Ofra Y, Buller M, Crump RW, Parker S, Frazier A, Crotty S, Zajonc DM, Peters B, **Xiang Y**. 2014. Potent neutralization of vaccinia virus by divergent murine antibodies targeting a common site of vulnerability in L1 protein. *J Virol*. 88(19):11339-55. PMID: 25031354
 - c. Sela-Culang I, Benhnia MR, Matho MH, Kaever T, Maybeno M, Schlossman A, Nimrod G, Li S, **Xiang Y**, Zajonc D, Crotty S, Ofra Y, Peters B. (2014) Mapping antibody epitopes based on antigen binding region complementarity. *Structure*. 22(4):646-57. PMID: 24631463
 - d. Matho MH, Schlossman A, Meng X, Benhnia MR, Kaever T, Buller M, Doronin K, Parker S, Peters B, Crotty S, **Xiang Y**, Zajonc DM. 2015. Structural and Functional Characterization of Anti-A33 Antibodies Reveal a Potent Cross-Species Orthopoxviruses Neutralizer. *PLoS Pathog*. 11(9):e1005148. PMID: 26325270

Complete List of Published Work in MyBibliography:

<http://www.ncbi.nlm.nih.gov/sites/myncbi/yan.xiang.1/bibliography/40946092/public/?sort=date&direction=ascending>

D. Research Support

Ongoing Research Support

5R01AI079217-07 Xiang (PI)

09/28/2008-03/31/2019

NIH/NIAID

Poxvirus Immune Evasion Mechanisms

The major goal of this project is to determine the immune evasion mechanisms of poxviruses and reveal novel aspects of interferon function.

Role: PI

Overlap: none.

R21AI133589 Xiang (PI)

7/1/2017-6/31/2019

NIH/NIAID

Non-vesicular lipid transport by poxvirus A6 protein

The major goals of this project are to determine the mechanism by which poxvirus manipulates cellular lipid transport for building its envelope.

Role: PI

Overlap: none.

Completed Research Support

R01AI081928 Deng (PI)

7/1/2009-6/31/2013 (no cost extension to 06/31/2014)

NIH/NIAID

Structure Function Studies on IL-18, IL-18 Binding Proteins and Receptors

The major goals of this project are to determine the structures of IL-18 receptor and binding proteins and to explore their binding mechanisms through functional studies.

Role: Co-I

Contract HHSN272200900048C Peters (PI)

9/30/2009-9/29/2014

NIH/NIAID

Targets of antibody responses in vaccinia virus & protection mechanisms

The goal of this contract is to identify novel B cell epitopes in vaccinia virus and elucidate novel mechanisms of antibody-mediated protection or pathogenesis.

Role: subcontractor

Xiang lab studies the interactions between host and pathogen with Zika virus and poxviruses as the model systems. There are a variety of projects available in the lab. The following are just some examples.

Zika virus (ZIKV) is an emerging pathogen for which there are no approved antivirals or vaccines. ZIKV infection in pregnant women is of major concern, as it is linked to catastrophic fetal abnormalities including microcephaly and spontaneous abortion. It is also associated with Guillain-Barre syndrome, a disorder characterized by immune-mediated demyelination of peripheral nerves. A key factor in ZIKV-associated pathologies is the observed tropism of ZIKV in neuronal cells and trophoblasts. Viruses encode limited number of proteins and their replication requires host factors. Identification of human factors that are essential for successful replication of ZIKV in neuronal cells and trophoblasts will provide potential targets for developing countermeasures against ZIKV. The overall goal of our project is to understand the host factors that determine the cellular tropism of ZIKV. To identify human factors that are essential for successful replication of ZIKV in neuronal cells, we will use Crispr-Cas9 genome editing technique to knock out human genes in the permissive (i.e., allow virus to replicate) neuronal cells. We will use SK-N-SH human neuroblastoma cell, as it is highly permissive for ZIKV replication. We will use a human genome-scale CRISPR-cas9 knockout library targeting 18,080 human genes to generate a library of SK-N-SH cells with various gene knockout. We will identify the genes that have been modified by CRISPR/cas9 through Illumina next-generation sequencing. We will further confirm the roles of these genes in viral replication by performing targeted gene knockout in SK-N-SH cells with CRISPR/Cas9 and testing permissiveness of the knockout cells for ZIKV. Furthermore, we will perform a similar human genome-wide Crispr/cas9 knockout screening to identify human factors that inhibit ZIKV replication. It is known that ZIKV is highly sensitive to interferons and replicates poorly in some human cells (nonpermissive cells). We will perform a human genome-wide knockout screen in nonpermissive cell to identify human intrinsic antiviral factors against ZIKV.

Poxviruses include some dangerous emerging or re-emerging pathogens as well as some promising vaccine vectors for infectious diseases and cancers. They are unique among viruses in that they encode a large number of proteins that are dedicated to evading host immune responses. These proteins include secreted inhibitors of cytokines as well as intracellular inhibitors of immune signaling or antiviral factors. The long-term goal of our project is to uncover the mechanisms of poxvirus immune evasion, which will reveal fundamental principles about virus-host interactions and provide knowledge for the development of vaccines and antivirals. Our recent work focuses on a family of ill-characterized tumor suppressor genes, SAMD9 and SAMD9L, which are also critical antiviral factors against poxviruses. We used CRISPR/cas9 knockout cells as well as knockout mice to study the role of SAMD9/SAMD9L in cancer development as well as antiviral responses.

The above two projects are just examples of projects available in the lab. A prospective student can choose to work on existing projects or a new project that custom-tailored to the mutual interest of the student and the PI. Every effort will be made to ensure the students gain a rewarding research experience.